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COMPARISON BAY LEAF (SYZYGIUM POLYANTHUM (WIGHT) WALP) EKSTRAKT WITH 400 MG AND 600MG DOSE ON LIPOPROTEIN(A) CONCENTRATION IN DYSLIPIDEMIC PATIENTS

Catur Prianwari*[1], Dharma Lindarto[2] & Santi Syafril[2]

[*1]Resident Department of Internal Medicine, Faculty of Medicine, University of North Sumatra
[2]Endrocrinology and Diabetes Division, Department of Internal Medicine, Faculty of Medicine, University of North Sumatra

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Abstract

Introduction: Dyslipidemia is a risk factor for cardiovascular disease. While Hyper Lipoprotein (a) is the main and independent risk factor for cardiovascular disease and aortic valve calcification stenosis. Synthetic anti-dyslipidemia drugs such as statin, niacin, mipomersen, and PCSK921 inhibitors had no clear evidence to reduce Lp(a) levels. Bay leaf ekstrakt was reported to have efficacy in lowering cholesterol and triglyceride levels, and was expected to reduce Lipoprotein(a).

Aim : to compare the effects of giving bay leaf ekstrakt at a dose of 400 mg and 600 mg to Lp (a) levels in dyslipidemia patients.

Method: This study was prospective design using clinical trial study. Study group I (n = 15) and control group II (n = 15) were chosen with double blinded random sampling. Data were obtained lipid profile and Lp (a) from blood sample which was taken before and after 30 days therapy. Data was analysed using T-dependent test with SPSS and $p < 0,05$ were considered significant.

Result: Lp (a) before therapy compared to after examination decreased in group I (25.52 + 31.36 vs 22.66 + 31.12) ng / dL; p = 0.001) and group II (27.81 + 33.79 vs 25.65+ 33.23) ng / dL; p value = 0.013), statistically significant in both group I and group II. The decrease in Lipoprotein (a) levels in group I was greater than in group II, and was statistikally significant (2.86 vs 2.17) mg / dL; p = 0.005).

Conclusion: The used of bay leaves (Syzygium polyanthum) extract 2 x @ 200 mg for 30 days reduced the levels of Lp(a) greater than 2x300 mg, and statistically significant

Introduction

Dyslipidemia is a lipid metabolism disorder characterized by an increase or decrease in plasma lipid fractions. The main abnormalities of lipid fraction are an increase in total cholesterol, LDL cholesterol, triglycerides, and a decrease in HDL cholesterol levels. apolipoprotein (a), which binds to disulfide bonds.[3] Several studies have suggested that there is an increase in Lp (a) levels in patients with dyslipidemia which is an independent risk factor for cardiovascular disease causing the number one death in the world.[4-5]

Some studies suggest that there are increased levels of Lp (a) in patients with dyslipidemia and is an independent risk factor in the occurrence of early coronary disease.[6] Overall from previous studies concluded there was no clear evidence that statin treatment to reduce levels of Lp (a).[7] Nowadays, therapy that can reduce Lp (a) significantly and quickly is apheresis lipoprotein (a) which is invasive and high cost makes this therapy ineffective and rarely done.[8]

Bay leaves contain tannin galat, galokatekin, flavonoids, saponins (triterpenoid), and essential oils (sesquiterpenes). Bay leaves also contain several vitamins, including vitamin A, vitamin C, vitamin E, thiamine, riboflavin, niacin, vitamin B6, vitamin B12, and folate. The results of in vitro studies showed that flavonoids work as inhibitors of the HMG-CoA reductase enzyme so that cholesterol synthesis decreases. An estimated 75 -

80% of people in developing countries and 25% in developed countries use traditional medicine as first-line treatment. [9-11]

Herbal medicine has long been practiced throughout the world. The potential market for herbal medicines and phytopharmaca in Indonesia is huge because Indonesia has more than 30,000 plant species and 940 of them are nutritious plants. Based on Permenkes No. 6 (2016) concerning formulary of native Indonesian herbal medicines, the level of security of bay leaf extract is quite high.[9,12]

In the subchronic toxicity test of bay leaf extract at a dose of 2 g / kg BW did not show any disturbance, at a dose of 3 g / kg BW showed an increase in plasma urea and creatinine levels and an increase in liver enzymes. Previous studies in patients with hypercholesterolemia or in mice reported that bay leaf extract (Syzygium polyanthum) reduced choleterol levels.[13]

This study analyzed the comparison of bay leaf extract with different doses to the effect of lipoprotein (a) levels in dyslipidemic patients.

METHODS

Study Samples
The target population is all dyslipidemic patients in Medan starting in June 2018 to March 2019.

Study Design
This research is a clinical trial with a prospective design. After getting Ethical Clearence, research subjects who includes the criteria are given an explanation and asked to give informed consent to participate in this study. Examination data were carried out on the 1st and 31st day, there are height (m), body weight (kg), BMI, LP (cm) and subjects were fasted for 10-12 hours and then blood samples were taken in the cubital fossa area examined in the laboratory are Lp (a), lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides), complete blood count, fasting blood glucose levels. In all puberty women, a urine pregnancy test is performed.

Then all subjects who includes the inclusion and exclusion criteria were randomized randomly selected and disguised into two groups, where there was group I is dyslipidemia patients who received bay leaf extract therapy 2 x 200 mg and group II is dyslipidemia patients who received extract therapy 2 x 300mg bay leaves for 30 days. Its monitored daily for compliance consuming bay leaf extract capsules for 30 days then compared the therapeutic effect based on levels of Lp (a), KT, LDL, HDL and TG.

Statistical Analysis
Univariate analysis was performed to determine the frequency distribution based on sociodemographic research subjects. Bivariate analysis used to compare groups I and II with the independent T test / Man Whitney U and the dependent T test / Wilcoxon statistically significant when p <0.05.

Table 1. Based on Formula used in capsules [4,5]

Grup	
I 2 x200mg	R/ Extract bay leaf 200 mg Amilum manihot 5% Amilum maydis 2,5% Laktosa ad 500 mg
II 2 x 300mg	R/ Extract bay leaf 300 mg Amilum manihot 5% Amilum maydis 2,5% Laktosa ad 500 mg

RESULTS

The research subjects were 30 people divided into two groups are group I is 15 people get bay leaf extract 2 x 200 mg and group II is 15 people group get bay leaf extract 2 x 300 mg. The basic characteristics of the research subjects are detailed in the table 4.1.

The subjects of this study found the majority of women in both group I and group II were [15 people (100%) vs. 14 people (93.3%), p = 0.952] with mean age (50.40 + 5.22 vs 50.07 + 4.73, p = 0.818) years, mean waist circumference of group I and group II (88.33 + 7.18 vs 92, 36 + 8.54) cm; p value = 0.207), mean height (1.56 + 0.04 vs 1.55 + 0.05) m; p value = 0.932), mean BW (67.00 + 10.65 vs 66.33 + 5.56) kg; p value = 0.787), BMI (27.54 + 3.22 vs 27.40 + 0.97) kg / m2; p value = 0.836), mean systolic blood pressure (118.33 + 5.23 vs 118.67 + 7.19) mmHg; p value = 0.928), mean diastolic blood pressure (77.33 + 4.58 vs 76.00 + 5.07) mmHg; p value = 0.446) but the results are not statistically significant.

The mean levels of LDL cholesterol in lipid profile such as group I and group II (22,55vs 175.73 + 155.00 + 35.40) mg / dL; p value = 0.066), HDL cholesterol (51.13 + 7.73vs 49.33 + 8.53) mg / dL; p value = 0.550), triglycerides (149.93 + 70.56 vs 202.80 + 114.57) mg / dL; p value = 0.193) and mean fasting blood glucose (94.20 + 15.03 vs 91.47 + 85.00) mg / dL; p = 0604) did not show statistically significant results.

In another lipid profile are mean total cholesterol between group I and group II (229.13 + 271.73 + 14.99 vs 52.17) mg / dL; p value = 0.005) and mean Lp (a) (25.52 + 31.36 vs 27.81 + 33.79) mg / dL; p value = 0.013), showing statistically significant results by getting higher total cholesterol and Lp (a) levels in group II.

Table 2. Characteristics of dyslipidemic patients in Medan

Variables	Group I 2x200 (n = 15)	Groups II 2x300 (n = 15)	p
Gender			
Female / Male	15 / 0	14/ 1	0.952
Age (tahun)	50.40 ± 5.22	50.07 ± 4.73	0.818
WS (cm)	88,33 ± 7,18	92,36 ± 8,54	0.207
H (m)	1,56 ± 0.04	1,55 ± 0,05	0.932
BW (kg)	67.00 ± 10.65	66.33± 5.56	0.787
BMI (kg/m^2)	27.54 ± 3.22	27.40 ± 0.97	0.836
SBP (mmHg)	118,33 ± 5,23	118,67 ± 7,19	0.928
DBP (mmHg)	77,33 ± 4,58	76,00 ± 5,07	0.446
TC (mg/dL)	229,13 ± 14,99	271,73 ± 52,17	0.005*
LDL (mg/dL)	155,00 ± 22,55	175,73 ± 35,40	0.066
HDL (mg/dL)	51,13 ± 7,73	49,33 ± 8,53	0.550
TG (mg/dL)	149,93 ± 70,56	202,80 ± 114,57	0.139
Lp(a)	25,52 ± 31,36	27,81 ± 33,79	0.013*
FGL (mg/dL)	94,20 ± 15,03	91,47 ± 85,00	0.604

Notes: WS: Waist size; H: Height; BW: Body Weight; BMI: Body Mass Index; TC: Total Cholesterol, LDL: *Low Density Lipoprotein*, HDL: *High Density Lipoprotein*, TG: Triglycerides, Lp(a): Lipoprotein a; FGL : Fasting Glucose Level.

Comparison of Lipoprotein(a) and lipid profiles levels between group I and group II detailed in table 4.2. In group I and group II, there was a statistically significant reduction in mean difference Lippoprotein(a) before and after treatment [(25.52 + 31.36 vs 22.66 + 31.12) ng / dL; p value = 0.001) and (27.81 + 33.79 vs 25.65 + 33.23) ng / dL; value of p = 0.013)]. The mean decrease in Lipoprotein (a) in group I than in group II, which was statistically significant (2.86 vs 2.17) mg / dL; p value = 0.005).

In group I and group II, there was a statistically significant reduction in total cholesterol before and after treatment [(229.13 + 14.99 vs 217.53 + 23.10) mg / dL; p value = 0.012) and (271.73 + 52.17 vs 225.93 +

30.80) mg / dL; value of p = 0.002)]. There was a decrease in total cholesterol in group I compared to in group II but not statistically significant (11.60 vs. 45.80) mg / dL; p value = 0.785).

In group I and group II, the mean decrease in LDL cholesterol before and after treatment [(155.00 + 22.55 vs 145.67 + 29.37) mg / dL; p value = 0.035) and (175.73 + 35.40 vs 145.72 + 33.10) mg / dL; p value = 0.001)]. There was a decrease in LDL cholesterol in group I compared to II but it was not statistically significant (9.33 vs 30.47) mg / dL; p value = 0.573).

In group I and group II there was a decrease in the mean HDL cholesterol before after treatment but it was not statistically significant [(51.13 + 7.73 vs 50.07 + 7.5) mg / dL; p value = 0.318) and (49.33 + 8.53vs 47.73 + 5.80) mg / dL; value of p = 0.344)]. There was a decrease in HDL cholesterol in group I than in group II were statistically significant (1.07 vs 1.60) mg / dL; p value = 0.019).

In group I and group II, the mean decrease in triglycerides before and after treatment was statistically significant [(149.93 + 70.56 vs 112.13 + 37.92) mg / dL; p value = 0.009) and (202.80 + 114.57 vs 138.60 + 49.76) mg / dL; value of p = 0.016)]. Enhancing decrease in triglycerides in group I than in group II, but it was not statistically significant (37.80 vs. 64.2) mg / dL; p value = 0.050).

Tabel 4.2 Comparison of Lipoprotein(a) and lipid profiles levels between group I and group II.

Variables	**Group (n = 15) Mean ± SD**				**Group II (n = 15) Mean ± SD**				**Δ*p***
	H_0	**H_{30}**	**Δ**	***p*a**	**H_0**	**H_{30}**	**Δ**	***p*b**	
Lipoprotein (a)	25,52 ± 31,36	22,66 ± 31,12	2,86	0,001 *	27,81 ± 33,79	25,65± 33,23	2,17	0,013 *	0,005 *
TC (mg/dL)	229,13 ± 14,99	217,53 ± 23,10	11,60	0,012 *	271,73 ± 52,17	225,93 ± 30,80	45,80	0,002 *	0,785
LDL (mg/dL)	155,00 ± 22,55	145,67 ± 29,37	9,33	0,035 *	175,73± 35,40	145,72 ± 33,10	30,47	0,001 *	0,573
HDL (mg/dL)	51,13 ± 7,73	50,07 ± 7,5	1,07	0,318	49,33 ± 8,53	47,73 ± 5,80	1,60	0,344	0,019 *
TG (mg/dL)	149,93 ± 70,56	112,13 ± 37,92	37,80	0,009 *	202,80 ± 114,57	138,60 ± 49,76	64,2	0,016 *	0,050

Notes: SD: Standard Deviation, ; TC: Total Cholesterol, LDL: *Low Density Lipoprotein*, HDL: *High Density Lipoprotein*, TG: Triglyseride, H_0: before being given extract, H_{30}: after being given extract for 30 days, delta: the difference between the results of the examination before being given the extract is reduced after being given the extract for 30 days, p_a: mean difference test H_0 and H_{30} treatment group, p_b: mean difference test H_0 and H_{30} control group, *: significant.

DISCUSSION

The results of this study indicate the decrease of Lp (a) levels by giving bay leaf extract 2x200 mg in group I and 2x300 mg in group II. In group I decreased Lp (a) Δ 2.86 (11.20%) by giving 2x200 bay leaf extract for 30 days and statistically significant (p = 0.001) and in group II decreased Lp (a) Δ 2, 17 (7.80%) by giving 2x300 bay leaf extract for 30 days and statistically significant (p = 0.005). There are differences in reduction of Lp (a) between group I and group II, as the reduction in Lp (a) in the first group is greater than group II (Δ 2.86 vs. Δ 2.17) and this difference was statistically significant (p = 0.005) . Previous research discusses the effect of bay leaf extract (Syzygium polyanthum) on the lipid profile, hs-CRP, Apo B, and ferritin, more detailed research about the effects of bay leaf extract (Syzygium polyanthum) directly reduces Lp (a) does not yet exist.[10,13]

Research by administering a combination of extracts of bitter (Andrographis paniculata) and bay leaf (Syzygium polyanthum) 2 x @ 150 mg compared with administration of simvastatin 1x20 mg for 30 days in 15 patients disipidemia been shown to reduce levels of hs-CRP and lipid profile more on providing a combination Bitter extract (Andrographis paniculata) and bay leaf (Syzygium polyanthum) rather than simvastatin 1 x 20 mg, but statistically not significant.[12]

Other studies in hyper Lp (a) patients and divided into 3 groups, group A (28 patients) received 20 mg / day simvastatin therapy, group B (29 patients) received atorvastatin 10 mg / day and group C (28 patients) received 5 mg rosuvastatin / day for 12 weeks. atorvastatin found to be most effective in reducing levels of Lp (a) levels with an average reduction of 18.73% ($p \leq 0.05$) from the base line. Whereas simvastatin and rosuvastatin only decreased levels of Lp (a) 3.15% and 8.58% from baseline and statistically not significant decline.[6]

Although niacin, mipomersen and PCSK921 inhibitors can reduce levels of Lp (a) about 20-30%, until now, no specific therapy or potent available to reduce Lp (a).[11] Overall of previous studies concluded there was no clear evidence that statin treatment to reduce levels of Lp (a) .[8] Currently, therapies that can lower Lp (a) significantly and quickly is Apheresis lipoprotein (a), by apheresis is decreasing Lp (a) 80% of the base line. Invasive and high costs make this therapy is not effective and rarely done. Currently in the research and development of Lp (a) Antisense oligonucleotides targeting apolipoprotein (a).[6]

It was concluded that the administration of bay leaf extract capsules (Syzygium polyanthum) at a dose of 2 x 200 mg in group I was higher than the administration (Syzygium polyanthum) at a dose of 2 x 300 mg in group II. So that the bay leaf extract capsules required (Syzygium polyanthum) with higher doses in patients who have high levels of Lp (a) is high.

This study showed a significant decrease in total cholesterol levels in giving bay leaf extract 2x200 mg in group I and 2x300 mg in group II (Δ 11.60, $p = 0.012$; and Δ 45.8; $p = 0.002$). There was a difference in decrease in total cholesterol between group I and group II, where the decrease in Lp (a) in group II was greater than group I (Δ 45.8 VS Δ 11.6) but it was not statistically significant ($p = 0.785$).

Besides total cholesterol, there was a decrease in LDL in 2x200 mg bay leaf extract in group I and 2x300 mg in group II. In group I decreased LDL Δ 9.33 with 2x200 bay leaf extract for 30 days and was statistically significant ($p = 0.035$) and in group B decreased LDL Δ 30.47 with 2x300 bay leaf extract for 30 days and statistically significant ($p = 0.001$). There was a difference in LDL reduction between group I and group II, where the decrease in LDL in group II was greater than group I (Δ30.47 VS Δ9.33) even statistically was not significant ($p = 0.573$).

The results of this study also showed a decrease in TG in bay leaf extract administration for 30 days at a dose of 2x200 mg in group I and 2x300 mg in group II showed a statistically significant both group I 2x200 mg (TG Δ 37.8; $p = 0.009$) and group II 2x300 mg (TG Δ 64.2 $p = 0.016$). There was a difference in TG reduction between group I and group II, where the decrease in TG in group II was greater than group I (Δ 64.2 VS Δ 37.8; $p = 0.050$) but it was not statistically significant.

In previous studies there was a greater decrease in lipid profile in group II by giving 2x300 bay leaf extract compared to group I by giving 2x200 bay leaf extract for 1 month. This is consistent with previous research on 25 male Wistar rats bay leafs concentrations of 5%, 10% and 20% has the effect of lowering total cholesterol and its potential equivalent to simvastatin.[10]

Likewise, another study by giving a combination of Sambiloto extract (Andrographis paniculata) and bay leaf (Syzygium polyanthum) for 30 days reduced lipid profile and ferritin levels better than simvastatin, but not statistically significant.[14] Other studies also concluded giving a combination of Sambiloto extract (Andrographis paniculata) and bay leaf (Syzygium polyanthum) 2 x 150 mg for 30 days in patients with dyslipidemia in addition to reducing lipid profile also decreasing Apo-B levels.[15]

Previous research reports that bay leaf contains several active substances that can reduce cholesterol and triglyceride levels, including: (1) flavonoids and tannins reduce cholesterol levels by inhibiting the enzyme HMG-Co A reductase which plays an important role in cholesterol biosynthesis so that the synthesis of apoB 100 decreases and the expression of LDL receptors on the surface of hepatocytes increases, blood LDL cholesterol will be uptake by hepatocytes to be metabolized resulting in decreased blood LDL cholesterol levels; (2) saponin increases the excretion of bile acids so that it increases the conversion of cholesterol to bile acids and is able to inhibit the absorption of cholesterol from food and bile acids in the intestine by forming complex bonds that do not dissolve.[16]

The limitation of this study, there are no uniform diet and physical activity on the research subjects so that can cause bias in the results of the study. In addition this study only provides treatmetn to patients who have dyslipidemia and not directly to patients who have hyper Lp (a).

CONCLUSION

Based on the results of this study, it was concluded that the administration of bay leaf extract (Syzygium polyanthum) for 30 days at a dose of 2x200 mg was significantly associated with reducing levels of Lipoprotein (a) compared with at a dose of 3x300 mg. To reduce the lipid profile by giving bay leaf extract (Syzygium polyanthum) at a dose of 2x300 mg greater than the dose of 2x200mg even not statistically significant.

SUGGESTION

Based on the results of this study are recommended for further study with subjects that are more specific, more stringent monitoring of dietary compliance, serial blood tests with longer treatment duration to obtain better results.

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